

Myocardial Injury and Long-term Mortality Following Moderate to Severe Carbon Monoxide Poisoning

Christopher R. Henry, BS

Daniel Satran, MD

Bruce Lindgren, MS

Cheryl Adkinson, MD

Caren I. Nicholson, RN

Timothy D. Henry, MD

CARBON MONOXIDE (CO) POISONING is a common cause of toxicological morbidity and mortality. From 1968 through 1998, the Centers for Disease Control and Prevention reported that CO poisoning contributed to an average of 1091 unintentional deaths and 2385 suicidal deaths per year in the United States.^{1,2} Although the annual death rate from CO poisoning has declined over time, CO remains the most common type of accidental poisoning in the United States, contributing to 40 000 emergency department visits annually.³ Carbon monoxide poisoning can occur with exposure to any source of combustion including automobile exhaust, fire, and defective heating systems.^{3,4}

Symptoms of CO poisoning include dizziness, nausea, weakness, headaches, lethargy, and confusion.^{3,4} The neurological consequences of CO poisoning have been described in detail.⁵⁻⁷ We recently reported that myocardial injury is a frequent consequence of moderate to severe CO poisoning, with 37% of patients having elevated cardiac biomarkers and/or diagnostic electrocardiogram changes.⁸ Despite the high frequency of myocardial injury, the

Context Carbon monoxide (CO) poisoning is a common cause of toxicological morbidity and mortality. Myocardial injury is a frequent consequence of moderate to severe CO poisoning. While the in-hospital mortality for these patients is low, the long-term outcome of myocardial injury in this setting is unknown.

Objective To determine the association between myocardial injury and long-term mortality in patients following moderate to severe CO poisoning.

Design, Setting, and Participants Prospective cohort study of 230 consecutive adult patients treated for moderate to severe CO poisoning with hyperbaric oxygen and admitted to the Hennepin County Medical Center, a regional center for treatment of CO poisoning, between January 1, 1994, and January 1, 2002. Follow-up was through November 11, 2005.

Main Outcome Measure All-cause mortality.

Results Myocardial injury (cardiac troponin I level ≥ 0.7 ng/mL or creatine kinase-MB level ≥ 5.0 ng/mL and/or diagnostic electrocardiogram changes) occurred in 85 (37%) of 230 patients. At a median follow-up of 7.6 years (range: in-hospital only to 11.8 years), there were 54 deaths (24%). Twelve of those deaths (5%) occurred in the hospital as a result of a combination of burn injury and anoxic brain injury (n=8) or cardiac arrest and anoxic brain injury (n=4). Among the 85 patients who sustained myocardial injury from CO poisoning, 32 (38%) eventually died compared with 22 (15%) of 145 patients who did not sustain myocardial injury (adjusted hazard ratio, 2.1; 95% confidence interval, 1.2-3.7; $P = .009$).

Conclusion Myocardial injury occurs frequently in patients hospitalized for moderate to severe CO poisoning and is a significant predictor of mortality.

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in-hospital mortality was low (5%). The long-term mortality for 230 consecutive patients following moderate to severe CO poisoning treated with hyperbaric oxygen therapy is reported herein.

METHODS

Hennepin County Medical Center is a Midwest regional center for the treatment of CO poisoning. The study population included 230 consecutive adult patients treated for moderate to severe CO poisoning with hyperbaric oxygen between January 1, 1994, and January

1, 2002. The study was approved by the institutional review board and procedures were in accordance with institu-

Author Affiliations: Minneapolis Heart Institute Foundation, Minneapolis, Minn (Mr C. Henry and Dr T. Henry); Departments of Internal Medicine (Drs Satran and T. Henry) and Emergency Medicine (Dr Adkinson and Ms Nicholson), Hennepin County Medical Center, Minneapolis, Minn; Department of Medicine, School of Medicine (Drs Satran and T. Henry) and Division of Biostatistics, School of Public Health (Mr Lindgren), University of Minnesota, Minneapolis; and Medical College of Wisconsin, Milwaukee (Mr C. Henry).

Corresponding Author: Timothy D. Henry, MD, Minneapolis Heart Institute Foundation, 920 E 28th St, Suite 40, Minneapolis, MN 55407 (henry003@umn.edu).

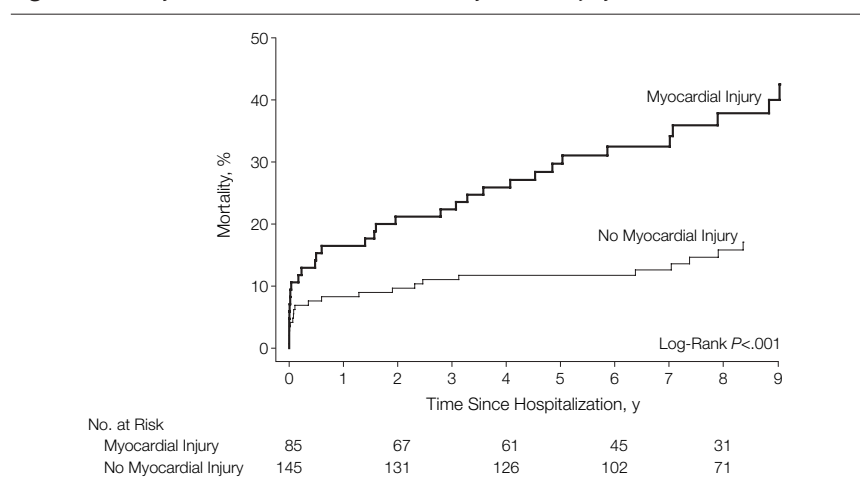
tional guidelines. Patients were included in the study if they were admitted to the hospital following hyperbaric oxygen treatment and were older than 18 years. Patient demographics, cardiovascular history, cardiac risk factors (diabetes, hypertension, smoking, family history of coronary artery disease, dyslipidemia), and cardiac biomarker data (levels of cardiac troponin I and creatine kinase-MB) from the comprehensive hyperbaric oxygen database were verified with the medical record. Baseline characteristics and in-hospital outcome have been reported previously.⁸

Long-term follow-up was completed using the Social Security Death Index with a censoring date of November 11, 2005. This index has been shown to be a highly accurate and specific source of mortality data.⁹⁻¹¹ Death certificates (if available) were analyzed for patients who died and deaths were classified in accordance with the 9th and 10th revisions of the *International Classification of Diseases*.^{12,13}

A standardized mortality ratio was calculated based on age- and sex-specific mortality rates from the United States life table for 2000.¹⁴ Univariable predictors of mortality were determined using the Kaplan-Meier method and the log-rank test for categorical variables (sex, diabetes, hypertension, smoking, dyslipidemia, previous history of myocardial infarction, previous revascularization, history of congestive heart failure, history of coronary artery disease, history of renal disease, suicidal vs accidental death, Glasgow Coma Scale score <15, intubation after CO poisoning occurred, cardiovascular medications administered at the time of CO poisoning, ischemia on electrocardiogram at the time of CO poisoning, and myocardial injury at the time of CO poisoning). For continuous variables (age and carboxyhemoglobin level), Cox regression was used to describe unadjusted associations with death. A stepwise multivariable Cox regression model was used to identify independent predictors of mortality.

In a supplementary analysis, a propensity score for myocardial injury was

Figure. Mortality of Patients With and Without Myocardial Injury



generated using nonparsimonious logistic regression modeling based on age, sex, diabetes, hypertension, smoking, dyslipidemia, Glasgow Coma Scale score of less than 15, and history of coronary artery disease and myocardial infarction. To assess adequacy of adjustment for baseline characteristics, patients were divided into 5 subgroups based on individual propensity scores with an equal number of patients in each subgroup.¹⁵ A second Cox regression model adjusted for propensity score was used to estimate myocardial injury as a risk for mortality; by adjusting for just 1 covariate, namely the propensity score, the risks of model overfitting and collinearity were minimized. All statistical analyses were performed using SAS software version 8.0 (SAS Institute Inc, Cary, NC); a 2-sided *P* value of less than .05 was considered significant.

RESULTS

For 230 consecutive patients, the mean age was 47.2 years and 166 (72%) were male. While 129 (56%) were active tobacco smokers, other cardiac risk factors were uncommon including only 52 (22.6%) with hypertension and 16 (7%) with diabetes. Previous cardiovascular disease was also uncommon with only 15 (6.5%) with prior myocardial infarction, 7 (3%) with prior congestive heart failure, and 6 (2.6%) with prior revas-

cularization.⁸ Initial CO poisoning was accidental in 135 (59%) patients, intentional (suicide attempt) in 91 (40%), and unclear in 4 (1%). Myocardial injury (defined by a cardiac troponin I level ≥ 0.7 ng/mL or creatine kinase-MB level ≥ 5.0 ng/mL) was frequent with 81 patients having elevated biomarkers (52 with abnormal troponin I, 29 with abnormal creatine kinase-MB) and an additional 4 patients having diagnostic electrocardiogram changes (biomarkers not available).⁸

Illness severity was high. One hundred seventeen patients (51%) were intubated after poisoning occurred, 187 (81%) experienced transient or persistent loss of consciousness, 182 (79%) had an abnormal Glasgow Coma Scale score (<15) on arrival at the medical center, 14 (6%) required intravenous medication for blood pressure support, and 27 (12%) required lidocaine or nitroglycerin. The median hospital stay for all patients was 3 days (interquartile range, 2-6 days).

Despite the severity of CO poisoning, in-hospital mortality was only 5% (12 patients). The most common cause of in-hospital death was a combination of burn injury and anoxic brain injury (8 patients). Four patients had cardiac arrest as a cause of anoxic brain injury and death.⁸ Of patients who sustained myocardial injury, 6 (7.1%) of 85 patients died in the hospital while

6 (4.1%) of 145 patients without myocardial injury died. An additional 42 patients died following hospital discharge for a total of 54 deaths (24%). The median follow-up was 7.6 years (range, in-hospital only to 11.8 years). The standardized mortality ratio was

3.0, indicating that this cohort was 3 times more likely to die during the follow-up period compared with age- and sex-specific US mortality rates.¹⁵

Overall, among the 85 patients who sustained myocardial injury from CO poisoning, 32 (38%) died compared

with 22 (15%) of 145 patients who did not sustain myocardial injury (FIGURE). Of the 32 patients with myocardial injury who died, 14 (44%) died of presumed cardiovascular causes (cardiac arrest, myocardial infarction, congestive heart failure, fatal arrhythmia, stroke, or natural causes in association with cardiovascular complications), 12 died of noncardiac causes (4 completed suicides, 13%), and 6 died of unknown causes. Of the 22 patients who did not sustain myocardial injury but died, only 4 (18%) died of presumed cardiovascular causes, 11 died of noncardiac causes (3 completed suicides, 14%), and 7 died of unknown causes.

Univariable analyses for predictors of long-term mortality appear in the TABLE. Significant predictors included age, diabetes, hypertension, history of coronary artery disease, history of congestive heart failure (only 7 patients), ischemia on electrocardiogram at time of CO poisoning, and myocardial injury at time of CO poisoning. Administration of cardiovascular medications (antiarrhythmic medications, β -blockers, or vasopressors) at the time of poisoning was also predictive but occurred almost entirely in patients with myocardial injury or ischemia on electrocardiogram.

Variables with an entry-level significance of $P < .10$ in the univariable analysis were included in a stepwise multivariable analysis, with the exception of cardiovascular medications (deemed to be collinear with myocardial injury) and previous congestive heart failure (7 patients). Only myocardial injury (adjusted hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.2-3.7; $P = .009$) and age (adjusted HR of 1.2 for every 5-year increase; 95% CI, 1.1-1.3; $P < .001$) were significant independent predictors. There was no significant interaction between myocardial injury and age and no evidence of a significant nonlinear association between age and survival. There was a significant interaction between follow-up time and age, which indicates nonproportionality of the effect of age

Table. Univariable Predictors of Long-term Mortality

	No. of Patients	No. (%) of Patients Who Died	5-y Survival Rate, % (95% CI)	P Value*
Sex				
Male	166	42 (25.3)	81.3 (75.4-87.2)	.36
Female	64	12 (18.8)	84.4 (75.5-93.3)	
Diabetes				
Yes	16	9 (56.3)	62.5 (38.8-86.2)	.001
No	214	45 (21.0)	83.6 (78.6-88.6)	
Hypertension				
Yes	52	18 (34.6)	76.9 (65.5-88.3)	.04
No	178	36 (20.2)	83.7 (78.3-89.1)	
Active smoker				
Yes	129	25 (19.4)	85.2 (79.0-91.4)	.09
No	101	29 (28.7)	78.2 (70.1-86.3)	
Dyslipidemia				
Yes	24	5 (20.8)	83.0 (68.4-98.2)	.79
No	206	49 (23.8)	82.0 (76.7-87.3)	
Prior event or procedure				
Myocardial infarction				
Yes	15	5 (33.3)	80.0 (59.8-100.0)	.35
No	215	49 (22.8)	82.3 (77.2-87.4)	
PCI or CABG surgery				
Yes	6	1 (20.0)	100 (NA)	.83
No	224	53 (23.6)	81.7 (76.7-86.8)	
Congestive heart failure				
Yes	7	6 (85.7)	57.1 (20.4-93.8)	<.001
No	223	48 (21.5)	82.9 (78.0-87.9)	
Coronary artery disease				
Yes	20	9 (45.0)	70.0 (49.9-90.1)	.03
No	210	45 (21.4)	83.3 (78.2-88.4)	
Type of CO poisoning				
Accidental	135	37 (27.4)	81.4 (74.8-88.0)	.13
Intentional	91	16 (17.6)	83.5 (75.7-91.3)	
Glasgow Coma Scale score				
15	46	6 (13.0)	93.5 (86.4-100.0)	.08
<15	182	47 (25.8)	79.6 (73.7-85.5)	
Intubation				
Yes	117	33 (28.2)	76.0 (68.2-83.8)	.06
No	113	21 (18.6)	88.5 (82.6-94.4)	
Intravenous cardiovascular medication				
Yes	38	20 (52.6)	55.3 (39.5-71.1)	<.001
No	192	34 (17.7)	87.5 (82.8-92.2)	
Ischemia on electrocardiogram				
Yes	69	26 (37.7)	69.4 (58.5-80.3)	.001
No	156	27 (17.3)	87.8 (82.7-92.9)	
Myocardial injury from CO				
Yes	85	32 (37.6)	71.6 (62.0-81.2)	<.001
No	145	22 (15.2)	88.3 (83.1-93.5)	

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CO, carbon monoxide; NA, not applicable;

PCI, percutaneous coronary intervention.

*Based on the log-rank test.

over the follow-up period, such that the risk of death due to age decreased over time.

In a supplementary propensity score analysis, the individual patient propensity scores for myocardial injury ranged from 0.04 to 0.94; the *c* statistic for the logistic model that generated the propensity score was 0.74. After adjustment for the propensity score, myocardial injury remained predictive of death (adjusted HR, 1.90; 95% CI, 1.02-3.37; *P* = .04).

COMMENT

Our results demonstrate that patients with myocardial injury from moderate to severe CO poisoning have substantially increased long-term mortality. Despite appearing to be a low-risk population from a cardiovascular standpoint, 37% of patients experienced acute myocardial injury and 38% of those with myocardial injury had died at a median follow-up of 7.6 years.

Carbon monoxide-mediated toxic injury results from a number of factors. Carbon monoxide binds to hemoglobin with an affinity 200 to 250 times that of oxygen so that exposure to CO, even in low concentrations, results in competitive binding to hemoglobin, reduced oxygen delivery, and profound tissue hypoxia.^{3,4} Carbon monoxide also binds to cytochrome-c oxidase (a terminal enzyme of electron transport chain), directly interfering with cellular respiration.^{16,17} These mechanisms are believed to cause neurological injury and likely contribute to myocardial injury as well.

Reports of long-term outcome in patients with acute CO poisoning are surprisingly limited. In a cohort of 138 patients from the United Kingdom in the 1960s, overall mortality was 15% at 3-year follow-up, but not all patients could be traced.^{18,19} Multiple studies document 1- to 6-month neurological outcomes following CO poisoning^{6,7,20-24} and several report long-term neurological outcome,²⁵⁻³⁰ but none discuss mortality. The most well-designed clinical trial of hyperbaric oxygen therapy in acute CO poi-

soning demonstrated improved neurological outcomes with hyperbaric oxygen at 6-week, 6-month, and 12-month follow-up, but mortality was not assessed.³¹ Thus, to the best of our knowledge, this is the first study to report mortality outcomes in patients hospitalized with moderate to severe CO poisoning. In the present study, 24% of patients died in a relatively young, healthy cohort at a median follow-up of 7.6 years, which was a mortality rate 3 times higher than expected compared with age- and sex-specific US mortality rates.

Our results are consistent with recent investigations showing that myocardial injury predicts short-term and long-term mortality in a wide variety of disease states. In acute coronary syndromes,³² sepsis,³³ pulmonary embolism,³⁴ and ischemic stroke,³⁵ elevated troponin levels predict short-term mortality. Increased long-term mortality with elevated troponin levels has also been demonstrated in acute coronary syndromes,³⁶ critical illness,³⁷ end-stage renal disease,³⁸⁻⁴⁰ and major vascular surgery.⁴¹ In our study, 37% of patients with CO poisoning had myocardial injury and 38% had died at a median follow-up of 7.6 years. While the precise mechanism for the increase in mortality is not clear, cardiovascular death was much more common (44% vs 18%) among patients who initially sustained myocardial injury. Because all patients in our study received hyperbaric oxygen therapy, it remains unclear if and what intervention can affect short-term and long-term outcomes of patients who experience myocardial injury from CO poisoning. It is also unclear if patients with milder forms of CO poisoning have a similar increase in mortality.

In conclusion, myocardial injury is a common consequence of moderate to severe CO poisoning and identifies patients at increased risk of mortality. Patients with suspected exposure to CO should be screened for myocardial injury, and further cardiovascular risk stratification should be considered in all patients with confirmed myocar-

dial injury. Although CO poisoning is the most common cause of accidental poisoning in adults in the United States, the focus has been on acute outcome, in particular the neurological manifestations. Our data indicate these patients have poor long-term outcome, a topic that deserves further study.

Author Contributions: Dr T. Henry had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: C. Henry, Satran, T. Henry. **Acquisition of data:** C. Henry, Satran, Adkinson, Nicholson, T. Henry.

Analysis and interpretation of data: C. Henry, Satran, Lindgren, Adkinson, T. Henry.

Drafting of the manuscript: C. Henry, Satran, Lindgren, T. Henry.

Critical revision of the manuscript for important intellectual content: C. Henry, Satran, Lindgren, Adkinson, Nicholson, T. Henry.

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There is a destiny that makes us brothers, none goes his way alone. All that we send into the lives of others comes back into our own.

—Edwin Markham (1852-1940)